Altitude exposure and increased heart rate: the role of the parasympathetic nervous system

Elevated heart rate (HR) has been demonstrated in response to acute hypoxia exposure, which is reportedly due to sympathetic nervous system activation (SNS) and concurrent withdrawal of parasympathetic nervous system activity (PSNS) (Koller *et al*, 1988). Although it is also known that this increased HR persists with chronic hypoxia exposure (Vogel *et al*, 1974), the mechanisms are less clear.

The authors discuss the conflicting research that presents itself within this area of research. Studies have shown that pharmacological inhibition of β-adrenergic receptors did not avert HR rise after 2-weeks of high altitude (HA) exposure (Hughson *et al.* 1994), implying the cause to be sustained PSNS withdrawal. Nevertheless, administration of muscarinic receptor antagonists increased HR after 9 weeks of HA exposure, suggesting increased PSNS activity (Boushel *et al.* 2001). It was speculated that these inconsistencies may be related to methodological considerations; particularly the inhibition of different receptor types, that merely one receptor was targeted per study, different subject groups and different exposure durations.

The readers were then led to the main objective of the study, which detailed how the authors would build upon existing knowledge by isolating the relative contributions of the SNS and PSNS, as well as the potential non-autonomic mechanisms contributing to increased HR in chronic hypoxia. The authors proposed that the increased HR associated with chronic hypoxia could be explained by a combination of both sympathoactivation and parasympathetic withdrawal and also hypothesised that a full cardiac autonomic blockade would eliminate HA-induced increases in HR.

In order to address this, seven male participants spent 4 weeks at 3454 m altitude, where all measurements were taken the week before ascent at sea level (SL) and over 2 days during the 15-18 days at HA. A number of haemodynamic parameters were analysed, alongside venous noradrenaline and arterial blood analysis. Measurements of such parameters were taken on the first day with no receptor inhibition being administered (CONT) and again following administration of glycopyrrolate (GLYC). On day two the measurements were taken after administration of propranolol (PROP), and again after additional administration of GLYC, forming the PROP+GLYC condition. Statistically a mixed model approach was employed to assess the effect of HA within the different drug conditions.

The results of this study showed a significant increase in HR from SL to HA during CONT (9.7 ± 7.9 bpm, P=0.007) and PROP (7.6 ± 4.0 bpm, P<0.001), but not during GLYC (2.3 ± 6.0 beats min^{-1}, P=0.28) and PROP+GLYC treatment (2.3 ± 5.4 beats min^{-1}, P=0.25). They also revealed the effect of HA on cardiac stroke volume and cardiac output depended on the type of receptor inhibition. Specifically stroke volume did not change significantly at HA during CONT treatment (–0.2 ± 19.2 ml, P=0.8) whereas a reduction was observed following PROP (–23.0 ± 13.4 ml, P<0.001), GLYC (–12.8 ± 11.9 ml, P=0.01) and PROP+GLYC treatments (–25.7 ± 16.1 ml, P<0.001). Cardiac output increased at HA during CONT treatment (1.1 ± 2.2 l min^{-1}, P=0.2) but was reduced following PROP (0.8 ± 0.8 l min^{-1}, P=0.02), GLYC (1.1 ± 1.1 l min^{-1}, P=0.02) and PROP+GLYC (2.0 ± 1.5 l min^{-1}, P=0.002). Furthermore venous noradrenaline rose by 245% from day 2 at HA to day 10 (1.1 nmol ± 0.5 vs. 2.7 ± 1.5 nmol l^{-1}, P=0.03), and by a further 11% at day 26 (3.0 ± 1.2 nmol l^{-1}, P=0.007). Mean arterial blood pressure (MAP) also increased at HA (P=0.001) however this was unaltered by any of the autonomic antagonists.

These results infer that cardiac parasympathetic withdrawal persists throughout HA acclimatisation and comprises the dominating cardioacceleratory mechanism, owing to the finding that increased HR was persistent when β-adrenergic, but not when muscarinic receptors were inhibited. The authors suggest that this may be the result of a reflex response to the activation of pulmonary stretch receptors by enhanced ventilation. The authors also suggest that the absence of a HA-induced increase in HR during combined inhibition of β-adrenergic and muscarinic receptors rules out a relevant contribution of a non-autonomic mechanism.

To our knowledge, this is the first study to provide novel findings related to the non-autonomous mechanism(s) responsible for sustained HR elevation with chronic HA exposure. The authors clearly state the research question and employ logical methodologies to tackle it, and discuss the findings in a scientifically-backed and concise manner. In general, the discussion is well-written, with many references made to previous research, which link with the literature they pose in their introduction.

They diligently state their study limitations, namely the small subject number and the lack of double—blindness. We came across some alternative critique that we wish to discuss in a constructive way, section by section.

The rationale of the drugs used and the fundamental pharmacokinetics have not been defined, making it difficult for readers to fully understand the logic. A brief description of each drug's purpose and action would have been useful.

The authors say that they preserved subjects' activity levels, but did not elaborate as to time/frequency stipulations and also gave no report of baseline levels. This is important to understand, as the hemodynamic parameters measured here are highly linked to training status, and the results reported may be reflective of that. Similarly, the authors did not elaborate on food and beverage consumption; specifically the absence of alcohol and caffeine intake in the preceding 24-hour period, likely to affect hemodynamics (Park and Ciffeli 2013).

With regards to the results, it is suggested that figure 2 graphs be slightly more elaborate; perhaps by adding coloured individual differences in order to distinguish between subject responses.

Systolic blood pressure forms the majority of the contribution to the MAP calculation, yet there was no mention of it; it would have been valuable to see to what extent this changed, and any change to the relationship with diastolic blood pressure. During the discussion the authors assume an absence of a decrease in stroke volume (SV) during the control is a false negative. However, little attempt is made at addressing the methodological limitation in which SV was obtained as a derived measure.

We believe that there could have been a clearer rationale as to the study objectives; hence we did not fully identify the meaningfulness behind it. It is clearly stated that HR is still elevated with chronic exposure to HA, but the authors do not explain why this is an issue, or what the clinical relevance is. We believe we are missing the "so what?" aspect, with regards to chronic HA exposure and elevated HR. There is still no mention of the issues associated with this, and what, if any, the applications may be. Does it matter that HR is elevated with chronic HA exposure? May this link to pathologies associated with HA, for instance by contributing to increasing pulmonary artery pressure that may in turn increase risk of

pulmonary odema? A more elaborate discussion on this aspect would have been beneficial in understanding the broader scientific relevance.

References

Boushel R, Calbet JA, Radegran G, Sondergaard H, Wagner PD & Saltin B (2001). Parasympathetic neural activity accounts for the lowering of exercise heart rate at high altitude. *Circulation* 104, 1785–1791.

Hughson RL, Yamamoto Y, McCullough RE, Sutton JR & Reeves JT (1994). Sympathetic and parasympathetic indicators of heart rate control at altitude studied by spectral analysis. *J Appl Physiol* 77, 2537–2542.

Koller EA, Drechsel S, Hess T, Macherel P & Boutellier U (1988). Effects of atropine and propranolol on the respiratory, circulatory, and ECG responses to high altitude in man. *Eur J Appl Physiol Occup Physiol* 57, 163–172.

Park KM, Cifelli CJ (2013). Dairy and blood pressure: a fresh look at the evidence. *Nutr Rev* **71**, 149-57.

Rose, M. S., C. S. Houston, C. S. Fulco, G. Coates, J. R. Sutton and A. Cymerman (1988). Operation Everest. II: Nutrition and body composition. *J Appl Physiol* 65, 2545-2551.

Vogel, J. A., Hartley, L. H., & Cruz, J. C. (1974). Cardiac output during exercise in altitude natives at sea level and high altitude. *J Appl Physiol*, *36*(2), 173-176.